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ORIGINAL REPORT

Cerebral Perfusion and Gray Matter Changes Associated With Chemotherapy-Induced Peripheral Neuropathy

Kelly N.H. Nudelman, Brenna C. McDonald, Yang Wang, Dori J. Smith, John D. West, Darren P. O'Neill, Noah R. Zanville, Victoria L. Champion, Bryan P. Schneider, and Andrew J. Saykin

Kelly N.H. Nudelman, Brenna C. McDonald, Yang Wang, Dori J. Smith, John D. West, Darren P. O'Neill, Victoria L. Champion, Bryan P. Schneider, and Andrew J. Saykin, Indiana University School of Medicine; Noah R. Zanville and Victoria L. Champion, Indiana University School of Nursing, Indianapolis, IN; and Yang Wang, Medical College of Wisconsin, Milwaukee, WI.

ABSTRACT

Purpose

To investigate the longitudinal relationship between chemotherapy-induced peripheral neuropathy (CIPN) symptoms (sx) and brain perfusion changes in patients with breast cancer. Interaction of CIPN-sx perfusion effects with known chemotherapy-associated gray matter density decrease was also assessed to elucidate the relationship between CIPN and previously reported cancer treatment–related brain structural changes.

Methods

Patients with breast cancer treated with (n = 24) or without (n = 23) chemotherapy underwent clinical examination and brain magnetic resonance imaging at the following three time points: before treatment (baseline), 1 month after treatment completion, and 1 year after the 1-month assessment. CIPN-sx were evaluated with the self-reported Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity four-item sensory-specific scale. Perfusion and gray matter density were assessed using voxel-based pulsed arterial spin labeling and morphometric analyses and tested for association with CIPN-sx in the patients who received chemotherapy.

Results

Patients who received chemotherapy reported significantly increased CIPN-sx from baseline to 1 month, with partial recovery by 1 year ($P < .001$). CIPN-sx increase from baseline to 1 month was significantly greater for patients who received chemotherapy compared with those who did not ($P = .001$). At 1 month, neuroimaging showed that for the group that received chemotherapy, CIPN-sx were positively associated with cerebral perfusion in the right superior frontal gyrus and cingulate gyrus, regions associated with pain processing ($P < .001$). Longitudinal magnetic resonance imaging analysis in the group receiving chemotherapy indicated that CIPN-sx and associated perfusion changes from baseline to 1 month were also positively correlated with gray matter density change ($P < .005$).

Conclusion

Peripheral neuropathy symptoms after systemic chemotherapy for breast cancer are associated with changes in cerebral perfusion and gray matter. The specific mechanisms warrant further investigation given the potential diagnostic and therapeutic implications.

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INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, potentially permanent adverse effect of breast cancer treatment.[1,2] In a meta-analysis of CIPN across many cancer types in 31 studies, CIPN was observed in 61% of patients 1 month after treatment, 60% of patients 3 months after treatment, and 30% of patients 6 months after treatment, indicating high prevalence as well as persistence of symptoms in a subgroup of patients.[3] CIPN may necessitate cancer treatment alterations, and currently, there are no effective treatments for symptoms.[4] Given the prevalence as well as evidence that CIPN may interfere with survivor quality of life,[4] further characterization of the biologic mechanisms driving CIPN may suggest potential novel approaches to treatment.

Despite various studies reporting changes in brain structure and function associated with other types of pain,[5-10] the impact of CIPN on brain structure and function has not been well studied. To date, there has been only one publication on this topic, which compared patients with multiple myeloma with CIPN to controls and found significant

differences in CIPN-associated brain activation during pain processing.[11] The relationship between CIPN and cerebral perfusion has not been specifically studied to date but could be valuable in identifying future CIPN treatment targets. We hypothesized that CIPN symptoms (CIPN-sx) in patients with breast cancer would be longitudinally associated with altered resting state cerebral perfusion. In addition, in view of our previous observations of altered cerebral perfusion and gray matter density after breast cancer chemotherapy treatment,[12-14] we investigated how these changes might relate to any CIPN-associated cerebral perfusion change.

METHODS

Participants

Written informed consent was obtained from all study participants using a protocol approved by the Indiana University Institutional Review Board in accordance with the Declaration of Helsinki. The female breast cancer cohort used for this study has been extensively described in previous publications.[13,14] For the current analyses, the sample consisted of patients treated with (n = 24) or without (n = 23) common, standard-dose chemotherapy regimens. Baseline assessment data were collected after surgery and before chemotherapy treatment for most individuals. Eight patients received neoadjuvant chemotherapy after their baseline assessment but before any definitive surgical treatment; these individuals did not differ significantly from the other patients who received chemotherapy regarding demographic factors, depression, or anxiety. The same assessments were also collected 1 month (1M) after chemotherapy treatment completion and 1 year (1Y) later (13 months after treatment), with yoked intervals for patients who did not receive chemotherapy. Group sizes were smaller (chemotherapy, n = 18; no chemotherapy, n = 19) for 1Y analyses as a result of missing CIPN-sx data and participant exclusion (discussed later). Only patients with noninvasive (stage 0) or nonmetastatic invasive (stage I, II, or III) disease were included. Besides metastatic disease, additional exclusion criteria for all participants included prior cancer, substance abuse, and other medical, neurologic, and psychiatric risk factors that might affect cerebral structure or function, as described in McDonald et al.[13]

	Table 1. Cohort Demographic and Clinical Characteristics, Rating Scales, and Cancer Treatment Data		
Characteristic	Patients Who Received Chemotherapy (1M, n = 24; 1Y, n = 18)	Patients Who Did Not Receive Chemotherapy (1M, n = 23; 1Y, n = 19)	P
Mean BL age, years (SD)	49.4 (7.9)	52.0 (9.1)	.312*
Mean BL education, years (SD)	15.3 (2.9)	15.4 (2.3)	.985*
Mean BL estimated full-scale IQ, Barona Index,[15] (SD)	109.9 (6.9)	111.2 (5.7)	.501*
White non-Hispanic, No. (%)	19 (79%)	21 (91%)	.226†
CES-D score, mean (SD)			
BL	9.2 (7.8)	7.3 (7.7)	.392*
1M	13.9 (8.4)	9.4 (9.6)	.088*
1Y	10.9 (7.5)	8.3 (9.9)	.401*
STAI-S score, mean (SD)			
BL	33.4 (13.9)	27.8 (7.7)	.098*
1M	34.8 (12.0)	31.2 (12.7)	.332*
1Y	30.8 (8.2)	28.8 (9.4)	.498*
Mean BL to 1M interscan interval, days (SD)	152.2 (63.1)	178.7 (74.1)	.192*
Mean 1M to 1Y interscan interval, days (SD)	379.5 (20.7)	371.8 (11.8)	.170*
Cancer stage, No. of patients (%)			
0 (DCIS)	0 (0)	5 (22)	.002†
I	11 (46)	16 (70)	
II	9 (38)	2 (9)	
III	4 (17)	0 (0)	
Therapy, No. of patients (%)			
Received radiotherapy by 1M	2 (8)	15 (65)	< .001†
Received radiotherapy by 1Y	11 (61)	12 (63)	.020†
On antiestrogen therapy at BL‡	0 (0)	1 (4)	.498†
On antiestrogen therapy at 1M‡	3 (13)	16 (70)	< .001†
On antiestrogen therapy at 1Y‡	8 (44)	15 (79)	.033†
Chemotherapy regimen§			
DOX/CYC/paclitaxel	7 (29)		
DOC/CYC	6 (25)		
DOC/carboplatin	6 (25)		
DOC/DOX/CYC	2 (8)		
DOC/cisplatin	1 (4)		
DOX/CYC	1 (4)		
Paclitaxel	1 (4)		

NOTE. Values calculated at BL unless otherwise noted.
Abbreviations: 1M, 1 month after chemotherapy treatment completion; 1Y, 1 year after 1M time point; BL, baseline (prechemotherapy treatment); CES-D, Center for Epidemiologic Studies–Depression; CYC, cyclophosphamide; DOC, docetaxel; DOX, doxorubicin; STAI-S, State Trait Anxiety Inventory–State.
*Analysis of variance.
†χ^2 test.
‡Antiestrogen therapies included tamoxifen (majority), anastrozole, letrozole, exemestane, raloxifene, and leuprolide acetate.
§Eight patients were also treated with trastuzumab, one was also treated with sunitinib, and one was also treated with bevacizumab.

Starting cohort
Ctx+ (n = 27)
Ctx– (n = 26)
HC (n = 26)
Individuals with BL/1M perfusion imaging data, as described in Nudelman et al, 2014

Excluded
HC: not assessed for CIPN (n = 26)
Ctx+: missing BL CIPN assessment (n = 2)
Ctx+: BL CIPN > 4 SD from mean (n = 1)
Ctx–: missing BL/1M CIPN assessment (n = 2)
Ctx–: pinched nerve (n = 1)

BL/1M Ctx+ (n = 24)

BL/1M Ctx– (n = 23)

Ctx+ excluded 1Y
Missing 1Y CIPN data (n = 5)
Missing 1Y perfusion scan (n = 2)

Ctx– excluded 1Y
Missing 1Y CIPN data (n = 4)

1Y Ctx+ (n = 18)

1Y Ctx– (n = 19)

Fig 1. CONSORT diagram. Number of individuals considered at each stage of the study, as well as number and reasons for excluded individuals. 1M, 1 month after chemotherapy treatment completion (or yoked interval for patients who did not receive chemotherapy and controls); 1Y, 1 year after 1M time point; BL, baseline (before chemotherapy treatment for the majority of patients); CIPN, chemotherapy-induced peripheral neuropathy; Ctx+, patients with breast cancer treated with chemotherapy; CTx–, patients with breast cancer treated without chemotherapy; HC, healthy controls; SD, standard deviation.

Demographic and treatment characteristics are listed in Table 1. The Center for Epidemiologic Studies–Depression Scale[16] and the State Trait Anxiety Inventory–State subscale[17] were used to measure depressive symptoms and anxiety. Between-group comparisons including analysis of variance (ANOVA), general linear models, and χ^2 tests were run with SPSS Statistics 21 (IBM Corporation, Somers, NY).

CIPN-sx were assessed using the self-report, validated Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (FACT/GOG-Ntx) four-item sensory-specific subscale.[18] Summed scores for each time point were generated. Given the specific nature of each included question, missing data were not imputed; if any question was unanswered, CIPN-sx total score was counted as missing. Exclusions from the cohort presented in Nudelman et al[14] comprised the following: for patients who received chemotherapy, two individuals were missing baseline CIPN-sx, and an additional six individuals were missing 1Y CIPN-sx; for patients who did not receive chemotherapy, two individuals were missing baseline or 1M CIPN-sx, and an additional four individuals were missing 1Y CIPN-sx. Two

additional individuals were excluded based on high baseline CIPN-sx: one patient who received adjuvant chemotherapy had CIPN-sx more than 4 standard deviations from the group mean at baseline, whereas one patient who did not receive chemotherapy with the highest CIPN-sx baseline score was noted to have a pinched nerve, requiring pain medication. Exclusion of these individuals yielded the final group sizes, presented earlier as well as in the CONSORT diagram (Fig 1).

Repeated measures ANOVA in SPSS was used to analyze CIPN-sx change over all three time points. In addition, ANOVA analyses at each time point contrasted CIPN-sx means between treatment groups. Finally, 1M – baseline CIPN-sx scores were analyzed in a two-way ANOVA to test for treatment group differences in change from baseline to after treatment.

Magnetic Resonance Imaging Acquisition

Cerebral perfusion scans were acquired with a Siemens Tim Trio 3T whole-body magnetic resonance imaging scanner (Siemens, Munich, Germany) using a 12-channel receiver-only head coil. During scan acquisition, patients were in a conscious resting state with closed eyes. Details of the scanning protocol used to obtain cerebral perfusion measurements have been previously published.[19] Briefly, a Q2TIPS pulsed arterial spin labeling sequence was applied using the proximal inversion with a control for off-resonance effects labeling scheme. Labeling was performed with an adiabatic inversion pulse with a 10-cm labeling region and 25-mm spacing from the distal edge of the labeled region to the image section, followed by optimized inversion time delays (TI_1 = 700 milliseconds and TI_2 = 1,800 milliseconds). These time delays were chosen to minimize 3-T intravascular signal intensity. Images were acquired using a gradient-echo single shot echo planar imaging readout with the following acquisition parameters: repetition time/echo time = 3,000/13 milliseconds, field of view = 224 mm, and matrix = 64 × 64. The imaging region consisted of 16 contiguous ascending axial slices of 7-mm thickness. Each perfusion measurement consists of 100 dynamic images (50 control and label image pairs) plus one M_0 image (the equilibrium brain tissue magnetization used to normalize the difference perfusion map), requiring a scan time of about 5 minutes. Head motion artifact was minimized using the scanner's built-in three-dimensional online prospective acquisition correction. High-resolution T1-weighted magnetization prepared rapid gradient echo (MPRAGE) images and high-resolution echo planar imaging whole-brain scans were acquired for subsequent reference and normalization. T2-weighted and fluid-attenuated inversion recovery sequences were acquired to check for incidental pathology. The high-resolution MPRAGE series for the analysis of gray matter density was acquired as previously described.[13]

Image Processing

Pulsed arterial spin labeling magnetic resonance imaging scan processing was performed using previously described methods.[19] Briefly, matched control images were subtracted from labeled images to create a perfusion-weighted time series; the results were used to create quantitative regional perfusion maps for each scan, which were normalized to Montréal Neurologic Institute space using SPM8 (Wellcome Department of Cognitive Neuroscience, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Scans were resampled to 2-mm³ voxels and smoothed with a 6 × 6
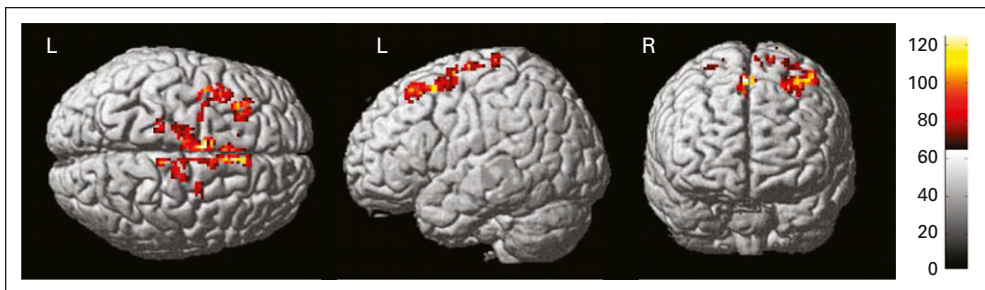
Fig 2. Chemotherapy-induced peripheral neuropathy symptoms (CIPN-sx) positively associated with perfusion. Surface rendering of the positive association of 1-month post-treatment perfusion with level of CIPN-sx reported at 1 month after treatment (P_{crit} < .001, k = 25); colored regions indicate increasing statistical significance, as shown on the color scale.

Table 2. CIPN-sx FACT/GOG-Ntx Four-Item Subscale Group Mean Values

	Mean (SD)		
Time Period	Patients Who Received Chemotherapy (1M, n = 24; 1Y, n = 18)	Patients Who Did Not Receive Chemotherapy (1M, n = 23; 1Y, n = 19)	P^*
BL CIPN-sx	0.46 (0.9)	1.09 (2.8)	.250
1M CIPN-sx	4.71 (5.0)	0.91 (1.4)	.001
1Y CIPN-sx	4.06 (3.4)	1.79 (2.5)	.027
$P\dagger$	< .001	.301	

Abbreviations: 1M, 1 month after chemotherapy treatment completion; 1Y, 1 year after 1M time point; BL, baseline (prechemotherapy treatment); CIPN-sx, chemotherapy-induced peripheral neuropathy symptom; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity; SD, standard deviation.
*P value for analysis of variance, between groups at each time.
†P value for repeated measures analysis of variance, within-treatment group change over three time points.

× 8 mm full width at half maximum kernel. Image processing of the MPRAGE series for analysis of gray matter density was performed as previously described.[13]

Image Analysis

To examine the potential roles of cerebral perfusion and gray matter in CIPN-related pain processing, all imaging analyses were limited to the group that received chemotherapy. First, time point analysis was performed to test for association of cerebral perfusion at 1M and 1Y with CIPN-sx at 1M and 1Y, respectively. For each time point, whole-brain perfusion scans were tested for association with the CIPN-sx variable using voxel-wise multiple regression imaging analysis in SPM8. A mask of regions of CIPN-sx–related perfusion at 1M was created for later use.

Second, baseline to 1M longitudinal analysis was performed to test for association of cerebral perfusion changes with CIPN-sx. Perfusion changes (1M – baseline scan images, obtained using the ImCalc utility in SPM8) were tested for association with CIPN-sx at 1M covarying for baseline, using voxel-wise multiple regression imaging analysis in SPM8. CIPN-sx scores at 1M covaried for baseline were used to examine the relationship between perfusion change and symptom severity, controlling for variance related to higher baseline symptom report unrelated to chemotherapy treatment. Mean values for the cluster identified in this analysis were extracted using MarsBar in SPM8, and 1M – baseline values were computed in SPSS to obtain CIPN-sx–associated perfusion cluster value changes[20] for later use.

Third, correlation analysis was performed for CIPN-sx and related perfusion changes with gray matter density frontal changes (reported in McDonald et al[13]). Mean values for the two frontal gray matter density clusters were obtained for each participant using MarsBar in SPM8. SPSS was then used to create an average of the two clusters for each participant, and 1M – baseline values were computed to obtain a single value for combined cluster change over time for each individual. Gray matter density cluster value changes were tested using SPSS for Pearson correlation with baseline to 1M changes in both CIPN-sx scores and perfusion cluster values (obtained in the second imaging analysis).

Fourth, image masking of the previously reported gray matter density-associated frontal perfusion decrease[14] observed in this cohort was performed to determine whether it occurred in CIPN-sx–related regions identified in the first imaging analysis. Multiple regression analysis of perfusion changes (1M – baseline scans, as in the second imaging analysis) with gray matter density cluster value baseline to 1M changes in SPM8 was masked with 1M CIPN-sx–related perfusion (from the first imaging analysis).

For the first three imaging analyses, to determine statistical significance and reduce noise, the voxel-wise critical significance threshold (P_{crit}) was set to .001 uncorrected, with a minimum cluster extent (k) of 25 voxels. For the fourth analysis, the uncorrected voxel-wise critical significance threshold was relaxed to $P_{crit} < .01$, k = 25, to identify any changes within the masked area. As presented in Nudelman et al,[14] demographic and other confounding variables such as caffeine consumption were previously considered for their potential impact on imaging analyses. These variables were not shown to be significant and are not included in the current analyses.

RESULTS

Demographic Analysis

Comparison of treatment factors, including radiation, antiestrogen therapy, and chemotherapy, as well as cancer stage, identified significant group differences (Table 1); given current treatment protocols, these differences are typical for this type of study. At baseline, there were no significant differences between groups in terms of age, education, intelligence quotient, and race/ethnicity. In addition, although a trend was observed for increased post-treatment depression in the chemotherapy
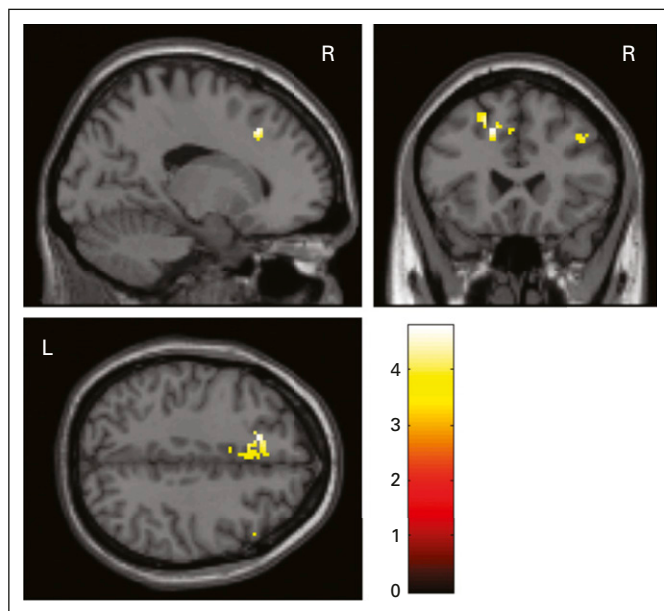
Fig 3. Chemotherapy-induced peripheral neuropathy symptoms (CIPN-sx) associated with perfusion increase. Colored regions of brain sections show areas with statistically significant association of baseline (before chemotherapy treatment) to 1-month post-treatment perfusion increase and 1-month post-treatment CIPN-sx covarying for baseline ($P_{crit} < .001$, k = 25); colored regions indicate increasing statistical significance, as shown on the color scale.
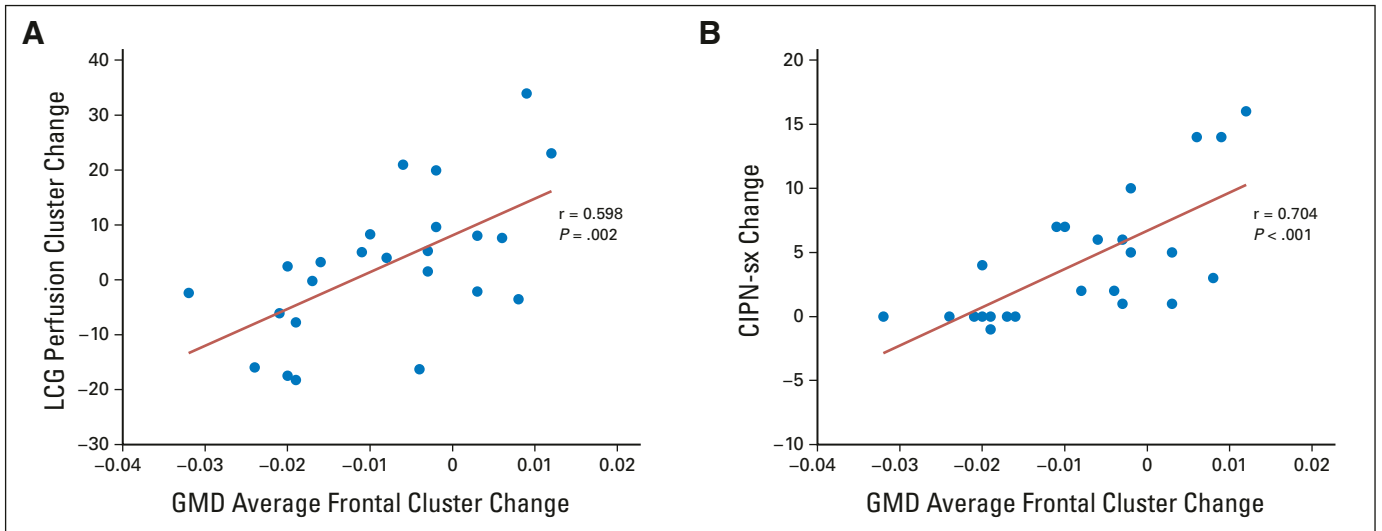
Fig 4. Gray matter density (GMD), perfusion, and chemotherapy-induced peripheral neuropathy symptom (CIPN-sx) change correlations. (A) Scatter plot of baseline (prechemotherapy treatment) to 1-month post-treatment (1M) change in GMD frontal clusters (as seen in McDonald et al[13]; x-axis) and the CIPN-sx–associated perfusion change cluster in the left cingulate gyrus (LCG). These variables showed a Pearson correlation ($r = 0.598$, $P = .002$), as labeled on the fit line. (B) Scatter plot of baseline to 1M change in GMD frontal clusters (x-axis) and CIPN-sx change. These variables showed a Pearson correlation ($r = 0.704$, $P < .001$), as labeled on the fit line.

group, there were no significant between-group differences for both baseline and 1M measures of depression and anxiety. Interscan intervals (approximately 5.5 months for baseline to 1M and 1 year for 1M to 1Y) did not differ significantly between groups. Finally, comparing patients who received adjuvant chemotherapy and those who received neoadjuvant chemotherapy, the eight patients who received neoadjuvant chemotherapy did not demonstrate any significant demographic differences.

Treatment Group CIPN-sx Analysis

At baseline, CIPN-sx for the chemotherapy and no chemotherapy groups were not significantly different (Table 2). At 1M and 1Y, patients in the chemotherapy group reported significantly more CIPN-sx than patients in the no chemotherapy group (1M, $P = .001$; 1Y, $P = .027$). Repeated measures analysis of all three time points for the chemotherapy group showed that these patients experienced significantly increased CIPN-sx over time ($P < .001$). In contrast, CIPN-sx did not increase significantly over time in patients who did not receive chemotherapy ($P = .301$). Finally, analysis of group differences in change in CIPN-sx from baseline to 1M showed that CIPN-sx increased significantly in chemotherapy patients compared with patients not treated with chemotherapy ($P = .001$).
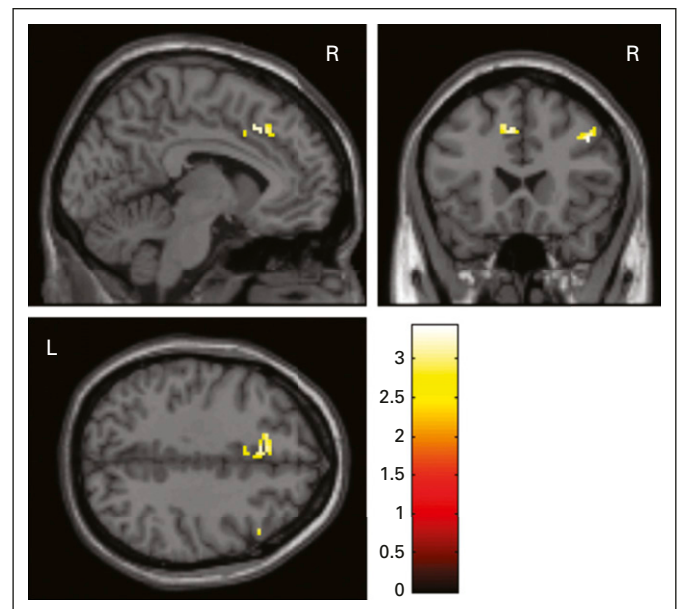
CIPN-sx–Associated Perfusion in Chemotherapy-Treated Patients

Time point analysis at 1M demonstrated that more CIPN-sx were associated with higher perfusion in several frontal region clusters, including bilateral superior frontal and cingulate gyri and left middle and medial frontal gyri ($P_{unc} < .001$; Fig 2; Appendix Table A1, online only). However, at 1Y, analysis of CIPN-sx with perfusion did not demonstrate any significant associations.

Longitudinal analysis indicated that more CIPN-sx at 1M, covaried for baseline, were also associated with increased perfusion from baseline to 1M. This increase was observed in several clusters including two regions identified in the 1M analysis, the left cingulate gyrus and left superior frontal gyrus (Fig 3, Table A1).

Gray Matter Density Correlation in Chemotherapy Patients

Baseline to 1M gray matter density change was positively associated with both baseline to 1M CIPN-sx change and perfusion cluster change (Fig 4), indicating that individuals with more baseline to 1M gray matter density decrease did not tend to show increased perfusion

Fig 5. Cerebral perfusion decrease associated with gray matter density decrease in chemotherapy-induced peripheral neuropathy symptom–related regions of interest. A mask of regions where chemotherapy-induced peripheral neuropathy symptoms correlated with perfusion at 1 month after chemotherapy completion superimposed on the analysis presented in Nudelman et al[14] of gray matter density frontal cluster change (baseline to 1 month after treatment) with perfusion change identifies clusters of overlap ($P_{crit} < .01$, $k = 25$) in the cingulate gyrus and superior frontal gyrus; colored regions indicate increasing statistical significance, as shown on the color scale.

and report increased CIPN-sx. Examination of the intersection of gray matter density-associated perfusion decrease and the mask of regions of perfusion associated with CIPN-sx at 1M showed overlap in the right superior frontal gyrus and left cingulate gyrus (Fig 5, Table A1).

DISCUSSION

To our knowledge, this is the first study to identify an association between cerebral resting state perfusion and CIPN-sx. Compared with patients who did not receive chemotherapy, patients with breast cancer treated with standard-dose chemotherapy exhibited significant post-treatment CIPN-sx. In the chemotherapy group, a significant association was observed between post-treatment CIPN-sx and perfusion in brain regions previously associated with pain processing in other populations. Specifically, the anterior cingulate region is known to be involved in pain processing, and this effect has been demonstrated in other pain populations and animal models.[7,8,21-26] Preliminary evidence in the literature shows that therapies targeting this region may alleviate pain, suggesting a potential future intervention.[27-30]

Although a significant association between cerebral perfusion and CIPN-sx was identified at 1M, a similar association was not observed at 1Y, which may be partly a result of a trend toward decreased CIPN-sx at this time. Alternatively, the changes in cerebral perfusion at 1M may reflect an acute pain processing mechanism, perhaps distinctly different from long-term chronic pain processing mechanisms.

Given the previously reported results of frontal gray matter density decrease and associated perfusion decrease observed in this cohort,[14] the impact of gray matter density change on CIPN-associated perfusion was also investigated. The association between gray matter density change, CIPN-sx, and perfusion change indicates that individuals showing gray matter density decrease may report less severe CIPN-sx while showing less CIPN-sx–related perfusion change. In this study, we also found that regions where perfusion correlated with CIPN-sx 1 month after chemotherapy completion overlapped with the previously reported[14] regions where decreased gray matter density was associated with decreased perfusion. Specifically, this overlap was apparent in the left cingulate gyrus and right superior frontal gyrus, where more CIPN-sx were associated with higher perfusion and where perfusion and gray matter density were positively correlated. This suggests that decreases in gray matter density may potentially interfere with CIPN-associated perfusion increase and reduce patient symptom report. This is particularly important because symptoms such as pain, numbness, and tingling are just one component of CIPN; deficits in motor reflexes, loss of dexterity, and issues with balance are also common. If chemotherapy-treated patients with gray matter density decrease do experience (and report) fewer symptoms compared with their non–gray matter density–affected counterparts, it

may mask identification and preclude intervention for potential threats to patient quality of life, occupational concerns, and CIPN-related safety concerns such as falls and accidents in the home, particularly in the elderly population.

Several limitations to this study should be noted. First, as with many neuroimaging studies in breast cancer, heterogeneous cancer stage and treatment modalities were an unavoidable limitation that must be addressed in future research. Second, although the study protocol asked participants to self-report CIPN-sx using a validated tool, the protocol did not include CIPN evaluation and grading by a clinician. Although this information would have aided in clinical interpretation of the results and their implications, the FACT/GOG-Ntx has been shown to be sensitive to treatment differences and change over time[18] and is comparable to other currently used scales.[31] The association of CIPN-sx with perfusion change in known pain processing regions reported here provides some convergent validation for the FACT/GOG-Ntx. A related limitation of this study is the absence of objective peripheral assessments of CIPN (eg, neurophysiologic testing, skin biopsy); filling this knowledge gap will be vital to a more comprehensive understanding of CIPN-related neuroanatomic and functional changes.

In summary, these results identify an objective cerebral neuroimaging perfusion measure associated with CIPN-sx. Identifying functional brain regions important to pain processing in this population may suggest future intervention targets for CIPN. Furthermore, these results suggest that gray matter density decrease and associated perfusion decrease may interfere with CIPN-sx–associated perfusion change and patient symptom perception, which are potentially clinically relevant findings because this could result in patient under-reporting of CIPN-sx. Future research should use objective peripheral measures of CIPN along with neuroimaging to further elucidate this mechanism and explore potential CIPN diagnostic and clinical implications.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Brenna C. McDonald, Andrew J. Saykin
Collection and assembly of data: Brenna C. McDonald, Yang Wang, Dori J. Smith, Darren P. O'Neill, Andrew J. Saykin
Data analysis and interpretation: Kelly N.H. Nudelman, Brenna C. McDonald, John D. West, Noah R. Zanville, Victoria L. Champion, Bryan P. Schneider, Andrew J. Saykin
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Table A1. Clusters of Significant* CBF									
Test	x†	y†	z†	k (cluster extent)	T Statistic	Z Statistic (derived from *P* value)	*P*‡	BA	Region
1M CBF, 1M CIPN-sx	−40	12	56	103	6.49	4.80	.131	6	L MiFG
1M CBF, 1M CIPN-sx	4	18	56	273	6.08	4.61	.020	8	R SFG
1M CBF, 1M CIPN-sx	−6	0	62	218	5.82	4.48	.035	6	L MFG
1M CBF, 1M CIPN-sx	−32	26	54	113	5.55	4.34	.115	8	L SFG
1M CBF, 1M CIPN-sx	−20	−30	74	36	4.89	3.98	.364	4	L PCG
1M CBF, 1M CIPN-sx	−10	18	42	157	4.89	3.98	.067	32	L CG
1M CBF, 1M CIPN-sx	20	−4	62	25	4.41	3.69	.453	6	R SG
1M CBF, 1M CIPN-sx	16	−30	42	25	4.39	3.68	.453	31	R CG
1M CBF, 1M CIPN-sx	−26	−2	66	30	4.39	3.68	.409	6	L MiFG
1M CBF, 1M CIPN-sx	−4	−14	32	37	4.06	3.47	.357	23	L CG
1M CBF, 1M CIPN-sx	−14	8	16	25	3.97	3.41	.453	NA	L Cau
1M-BL CBF, 1M c BL CIPN-sx	−16	24	42	179	4.76	3.87	.040	32	L CG
1M-BL CBF, 1M c BL CIPN-sx	36	−98	−12	27	4.72	3.85	.402	18	R IOG
1M-BL CBF, 1M c BL CIPN-sx	44	22	36	25	4.18	3.53	.420	9	R MiFG
1M-BL CBF, 1M c BL CIPN-sx	−4	6	54	31	4.06	3.45	.368	6	L SFG
1M-BL CBF, 1M–BL GMD	−40	10	58	67	5.06	4.13	.436	6	L MiFG
1M-BL CBF, 1M–BL GMD	−30	30	54	39	3.38	3.03	.561	8	L SFG
1M-BL CBF, 1M–BL GMD	−6	22	40	55	3.22	2.91	.483	32	L CG
1M-BL CBF, 1M–BL GMD	4	16	54	63	2.92	2.67	.451	8	R SFG

Abbreviations: 1M, 1 month after chemotherapy treatment completion; 1 M c BL, 1 M covarying for BL; BA, Brodmann area; BL, baseline (prechemotherapy treatment); Cau, caudate; CBF, cerebral blood flow; CG, cingulate gyrus; IOG, inferior occipital gyrus; L, left; MFG, medial frontal gyrus; MiFG, middle frontal gyrus; NA, not available; PCG, precentral gyrus; R, right; SFG, superior frontal gyrus; SG, subgyral.
*Chemotherapy-induced peripheral neuropathy symptom (CIPN-sx) –associated perfusion tests used voxel-wise $P_{crit} < .001$, k = 25; GMD-associated perfusion tests used $P_{crit} < .01$, k = 25.
†Montreal Neurological Institute and Hospital coordinates.
‡Cluster-level uncorrected *P* values.